The Effect of Obesity on the Time to Recurrence in Ovarian Cancer: A Retrospective Study

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Abstract

The aim of this study was to determine the effect of obesity on recurrence time in ovarian cancer. This was a multicenter, retrospective chart review of 370 patients. The median time to recurrence was 15 months in obese and nonobese patients. Obesity does not affect the time to recurrence or progression-free survival in patients with ovarian cancer.

Introduction/Background: The objective of this study was to examine whether obesity affects the time to recurrence in primary epithelial ovarian cancer. **Patients and Methods:** A multicenter retrospective chart review was performed between 2004 and 2009. Three hundred seventy patients were eligible for analysis. Demographic and clinicopathological variables and treatment-related data were collected. Women with a body mass index (BMI) > 30 were categorized as obese. The time to recurrence was quantified in terms of months. Survival analyses were performed using the Kaplan-Meier method and compared using log-rank testing. **Results:** One hundred thirty (35%) obese patients were compared with 240 (65%) nonobese patients. A recurrence was documented in 125 (47.9%) nonobese patients and 49 (37.7%) obese patients. Time to recurrence between both BMI groups was identical, at 15 months ($P = 1.0$). The progression-free survival was similar in obese and nonobese subjects ($P = .118$). **Conclusion:** Obesity does not affect the recurrence time in patients with primary ovarian cancer.

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Introduction

The prevalence of obesity in adults in the United States is 35.6%.[1] This condition has been associated with an increased risk of several types of cancers, including breast and ovarian cancer, and research indicates that obesity contributes 14% to 20% of cancer-related mortality.[2] Ovarian cancer is the fifth leading cause of cancer deaths in women according to cancer statistics reported by the American Cancer Society in 2012. This accounts for 6% of cancer related deaths in women.[3] Approximately 12% of patients with ovarian cancer are obese.[4] Burke and Morris reported that 60% of patients with advanced ovarian epithelial cancer will develop recurrent disease after initial diagnosis treatment.[5] Management of ovarian cancer is highly dependent on response to degree of tumor debulking[6] and chemotherapy[7]; modifiable prognostic factors are limited.[8] Obesity is a common and potentially modifiable prognostic factor.

Obesity affects the body's hormonal balance. Ovarian cancer has been shown to have some degree of hormonal responsiveness.[9] There is clinical and biochemical evidence supporting the therapeutic role of hormonal agents in ovarian cancer treatment such as: tamoxifen,[10] aromatase inhibitors,[11] gonadotropin modulators,[12] and progestins.[13] In addition, Risch documented abnormal androgen homeostasis in ovarian cancer.[14] Obesity represents a hyperandrogenic and hyperestrogenic state. Increased peripheral production of androgens and estrogens in adipose tissue and decreased sex hormone-binding globulin results in increased free testosterone and estrone. Additionally, adipose tissue concentrates lipid-soluble steroids, contributing to increased androgen clearance and an extremely enlarged total body steroid pool.[15] Li et al[16] hypothesized that hyperandrogenism mediated by obesity in the presence of certain androgen receptor polymorphisms might promote aggressive epithelial ovarian cancer biology.

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Few studies have examined obesity as a prognostic factor for time to recurrence in ovarian cancer.[6,7,17-20] Thus, the primary aim of this study was to investigate the relationship between obesity and progression-free survival among a cohort of women diagnosed with ovarian cancer. It was hypothesized that obese ovarian cancer patients would have greater rates of recurrence compared with nonobese patients.

Patients and Methods

A multicenter retrospective study was performed at Mercy Medical Center in Baltimore, Maryland and University of Michigan Medical Center in Ann Arbor, Michigan, on all patients with primary epithelial ovarian cancer diagnosed between 2004 and 2009 (n = 591). The study was approved by the Institutional Review Board at both institutions.

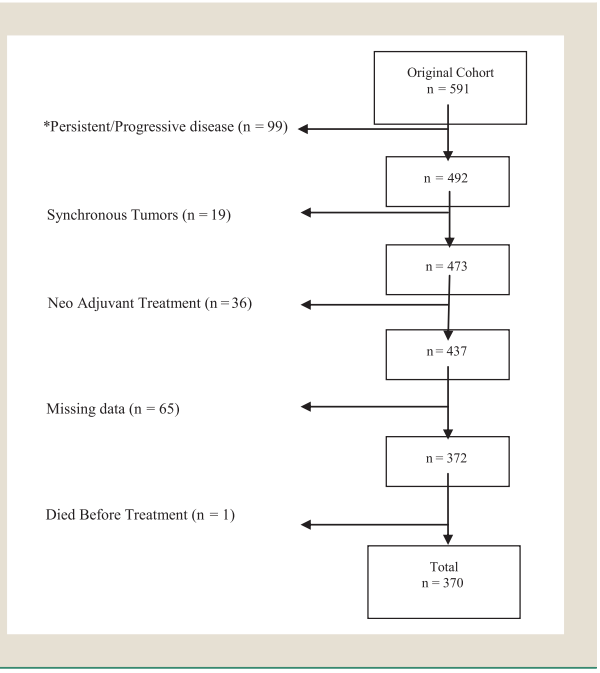
All data were abstracted from the patient's medical records. Preoperative height and weight data were collected from medical charts, measurements within 1 month after surgery were also permissible if preoperative values were not available. Body mass was calculated and patients were categorized according to their body mass index (BMI) based on the definitions set forth by the Classification of Overweight and Obesity by BMI (World Health Organization, 2004).[21] Patients were classified as obese if they had a BMI $\geq$ 30, or nonobese if they had a BMI $<$ 30.

Abstracted covariates included age, medical comorbidities, stage, and histology. Preoperative comorbidity data collected included: hypertension, diabetes, coronary heart disease, and pulmonary disease such as asthma or chronic obstructive pulmonary disease. Treatment-related data such as number of cycles of adjuvant chemotherapy, and optimal versus suboptimal tumor debulking, were also collected. Optimal debulking was defined as the presence of residual implants $<$ 1 cm, in accordance with the definition set forth by the Gynecologic Oncology Group.[22] The diagnosis of recurrence was made according to positive clinical, radiologic, or serologic evidence of recurrence. Time to recurrence was then quantified in terms of months from initial surgery.

Patients who did not have a complete clinical, radiological, and serologic response to surgical debulking and adjuvant chemotherapy were classified as having persistent or progressive disease and were excluded from this analysis [n = 99]. In addition, patients who died after surgery, before adjuvant chemotherapy treatment was completed, those who were lost to follow-up, or had missing requisite data to determine the diagnosis of recurrence or a disease-free interval were also excluded from the analysis. Patients with synchronous tumors were also excluded. Those without data sufficient to calculate BMI or for whom follow-up data were not obtainable from the chart were also excluded from review. Patients who received neoadjuvant chemotherapy were also excluded, to maintain homogeneity of the sample population.

Differences in the characteristics between BMI groups were analyzed using χ^2 test and Fisher exact test for categorical variables. Continuous variables were analyzed using Student *t* test, and Mann-Whitney *U* test. The Kolmogrov-Smirnov method was used for testing normality. Kaplan-Meier curves with log-rank testing were used for survival analysis. Multivariate models were assessed using Cox regression. All statistical analyses were performed using Stata Software (version 12, College Station, TX).

Figure 1 Study Population With Exclusions



* These 99 patients who progressed or had persistent disease while receiving adjuvant chemotherapy were excluded from the primary analysis because they had no disease-free interval, so time to recurrence could not be defined, which was our primary outcome. They were analyzed separately and there was no difference in the proportion of obese patients when compared with the study population (P = .88).

Results

Five hundred ninety-one persons were diagnosed with primary epithelial ovarian cancer and treated between 2004 and 2009 at both institutions. Of those, 16.8% (n = 99) had persistent or progressive disease, 11% (n = 65) had missing requisite data, 3.2% (n = 19) had synchronous tumors, 6% (n = 36) underwent neoadjuvant chemotherapy, and 2 patients died shortly after surgery. The remaining sample size was n = 370 (Fig. 1).

Three hundred seventy patients who met the inclusion criteria were identified. Demographic and clinicopathological data of the population are shown in Table 1. Approximately 35%, n = 130 of the patients were classified as obese. Obesity did not vary by age or race (P = .46 and .57, respectively). Most patients were diagnosed at stage III (51.6%, n = 191), and histology was predominantly papillary serous (51%, n = 189). Neither stage nor histologic subtype varied according to obesity (P = .6 and .21, respectively). Pulmonary disease, hypertension, and diabetes were more prevalent in the obese population (P = .03, .001, and $<$ .001, respectively).

Treatment for obese and nonobese patients was similar. Most received optimal debulking (70%, n = 259) and had 6 or more cycles of standard adjuvant chemotherapy (71%, n = 261). Treatment data are given in Table 2. Of the patients whose disease recurred in the study population; there was no difference in the platinum sensitivity between obese and nonobese patients (83.3% vs. 77.3%; P = .633).

The progression-free survival curves for both patient groups were similar (P = .11). There was no difference in the incidence of recurrence between nonobese and obese patients (47.9% vs. 37.7%;

Table 1 Patient Demographic and Clinicopathological Factors Stratified According to BMI

Factor	BMI <30 (n = 240)	BMI ≥30 (n = 130)	P[a]
BMI Range	15-29	30-66	
Mean Age (SD), Years	58.2 (12.2)	57.3 (10.5)	.463
Race, n (%)			.573
Nonwhite	20 (8.3)	13 (10.0)	
White	220 (91.7)	117 (90.0)	
Stage, n (%)[b]			.607
I	54 (22.5)	32 (24.6)	
II	36 (15.0)	23 (17.7)	
III	125 (52.1)	66 (50.8)	
IV	21 (8.8)	7 (5.4)	
Unstaged	4 (1.7)	2 (1.5)	
Grade, n (%)			.846
1	29 (12.1)	20 (15.4)	
2	34 (14.2)	18 (13.8)	
3	122 (50.8)	64 (49.2)	
Missing	55 (22.9)	28 (21.5)	
Histology, n (%)			.214
Serous	133 (55.4)	56 (43.1)	
Clear cell	9 (3.8)	11 (8.5)	
Endometrioid	38 (15.8)	20 (15.4)	
Mucinous	21 (8.8)	19 (14.6)	
Mixed	8 (3.3)	4 (3.1)	
Other	17 (7)	13(10)	
Undifferentiated	14 (5.8)	7 (5.4)	
Pulmonary Disease, n (%)			.030
Yes	9 (3.8)	12 (9.2)	
No	231 (96.3)	118 (90.8)	
Hypertension, n (%)			.001
Yes	77 (32.1)	66 (50.8)	
No	163 (67.9)	64 (49.2)	
Coronary Heart Disease, n (%)			.141
Yes	14 (5.8)	13 (10.0)	
No	226 (94.2)	117 (90.0)	
Diabetes, n (%)			<.001
Yes	14 (5.8)	31 (23.8)	
No	226 (64.2)	99 (76.2)	

Abbreviations: BMI = body mass index, calculated as weight (kg)/height (m^2); FIGO = International Federation of Gynecology and Obstetrics.
[a]Significance $P < .05$. P was calculated using χ^2 and Fisher exact test, and Student t test where appropriate.
[b]Stages I to IV according to the FIGO staging system.

$P = .06$). Median time to recurrence was 15 months in both groups ($P = 1.0$). Recurrence data are shown in Table 3 and survival curves are given in Figure 2.

There were no differences in the time to recurrence or progression-free survival when BMI was subclassified into underweight, normal, overweight, and obese (classes I, II, and III) in accordance with the WHO 2004 criteria.[21] A multivariate model including pulmonary disease, hypertension, and diabetes, the covariates that were significantly different according to obesity status, was explored using Cox regression. However, these covariates had no statistically significant effect on differences in recurrence and substantive findings remained unchanged. Further and additional Cox regression analysis was performed adjusting for International Federation of Gynecology and Obstetrics stage, debulking status, and BMI, which showed no difference in the time to recurrence.

Table 2 Surgical Outcomes Stratified According to BMI

Variable	BMI <30 (n = 240)	BMI ≥30 (n = 130)	P[a]
Number of Chemotherapy Cycles, n (%)			.469
<6	44 (68.8)	20 (31.3)	
≥6	166 (63.6)	95 (36.4)	
Missing	30 (66.7)	15 (33.3)	
Debulking Status, n (%)			.663
Optimal	169 (70.4)	90 (69.2)	
Suboptimal	55 (22.9)	28 (21.5)	
Missing	16 (6.7)	12 (9.2)	

Abbreviation: BMI = body mass index, calculated as weight (kg)/height (m^2).
[a]Significance $P < .05$. P was calculated using χ^2 and Fisher exact test, and Student t test where appropriate.

Discussion

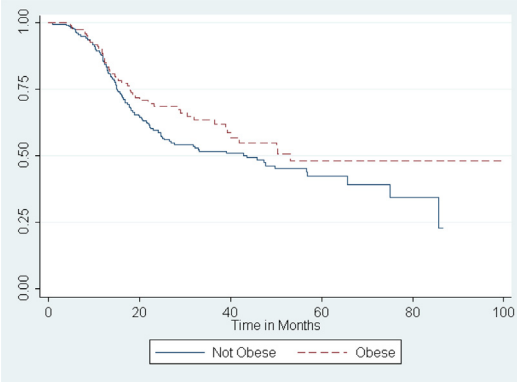
The effect of obesity on survival in ovarian cancer has been investigated in other studies with conflicting results.[6,7,17-20] Pavelka et al noted a shorter time to recurrence in obese patients. However, this study was limited by the sample size, which consisted of 31 patients with a BMI of ≥ 30.[18] In their study, Matthews et al found a statistically significant decrease in the rate of recurrence in obese patients (68% vs. 79%; $P = .04$) and no difference in progression-free survival (17 vs. 11 months; $P = .14$). This study had a larger sample size consisting of 304 patients with 71 obese patients. They concluded that obesity did not have an effect on time to recurrence when patients were optimally debulked.[6] Barrett et al investigated progression-free survival and overall survival in 1067 patients who participated in the SCOTROC 1 (Scottish Randomized Trial in Ovarian Cancer 1) trial. There were 130 obese patients in this population which is comparable with our sample size. They concluded that obesity

Table 3 Recurrence Data According to BMI

Variable	BMI <30 (n = 240)	BMI ≥30 (n = 130)	P
Recurrence, n (%)			.118[a]
Yes	115 (47.9)	49 (7.7)	
No	125 (52.1)	81 (62.3)	
Median Recurrence Time (IQR), Months	15 (10)	15 (17)	.987[b]

Abbreviation: BMI = body mass index, calculated as weight (kg)/height (m^2); IQR = interquartile range.
[a]χ^2 test.
[b]Mann-Whitney U test.

Figure 2 Progression-Free Survival



was not associated with a poorer prognosis in patients who received chemotherapy based on their measured glomerular filtration rate and actual body weight.[7] The patients in our study received chemotherapy doses based on their actual body weight and the doses were not capped. This approach has been found to be safe and efficacious in obese patients with other cancers.[23] It was also recently reinforced according to the most recent guidelines put forth by the American Society of Clinical Oncology. These guidelines state that ideal body weight should be used to calculate the appropriate chemotherapy doses in obese patients.[24] A Swedish study by Skirnisdottir and Sorbe[19] had a large sample size of 635 patients with 75 obese patients. This study showed no significant differences in recurrence-free survival across all BMI subgroups. The 5-year recurrence-free survival of the complete series was 72%. However, this study investigated patients at only early-stage epithelial ovarian cancer despite the fact that most patients present with advanced-stage disease. A more recent study by Skirnisdottir and Sorbe showed that patients who were underweight with serous histology had poorer survival outcomes.[20]

Our study consisted of 370 patients with primary ovarian cancer, 130 of whom were obese. There was no statistical difference noted in demographic or clinicopathological factors between obese and nonobese subjects. However, there was a high prevalence of medical comorbidities in the obese group, which was expected because obesity is a well established risk factor for these medical conditions related to obesity. Results of this study showed that there was no statistically significant difference in the disease-free interval or progression-free survival between obese and nonobese patients. It is important to note that we intentionally excluded patients with persistent or progressive disease, because we were specifically investigating the time to disease recurrence and progression-free survival in obese patients with ovarian cancer. To evaluate these parameters, the patients who showed any evidence of residual disease based on clinical, radiological, or serological data after surgical staging and standard adjuvant chemotherapy were excluded from the study. We acknowledge that this would be a useful data set to investigate in evaluation of overall survival in this patient population.

In a review article, Risch concluded that there was evidence supporting the role of androgens and progesterone in etiology of ovarian cancer.[14] Obesity is thought to result in a hyperandrogenic state.[15] Lipid-soluble hormones such as androgens, estrogens, and progesterone are sequestered in adipose tissue, significantly increasing the total body steroid pool. There is also some evidence to suggest that there is an upregulation of adrenocortical steroidogenesis resulting in increased androgen secretion in obese subjects.[15] Li et al[16] reported that hyperandrogenism mediated by obesity in the presence of certain androgen receptor polymorphisms might promote aggressive epithelial ovarian cancer biology. Obesity has been shown to be an in important risk factor in tumor carcinogenesis in several types of cancers.[25] However, no definitive humoral etiology has been established for ovarian cancer, unlike endometrial cancer, which has a well established hormonal etiology.[26] Findings from this study do not give clinical support to the fact that tumor biology is negatively affected by the hormonal changes related to obesity.

The strengths of our study include the large overall sample size, and one of the largest populations of obese patients who have been investigated in examination of the effect of obesity on the time to disease recurrence in primary epithelial ovarian cancer. The population was very homogenous and stringent exclusion criteria were used. In this study, we investigated a broader population of ovarian cancer patients, including all stages of cancer. Weaknesses include that this was a retrospective study. Also, BMI was calculated at the time of diagnosis and presentation to the gynecologic oncologist, which would take into account ascites as part of body weight. Other studies have used BMI at the time of postoperative visit[18] or the time of administering the first cycle of adjuvant chemotherapy.[7]

Conclusion

Our findings suggest that obesity does not affect the time to disease recurrence or progression-free survival in patients with ovarian cancer. These clinical findings are in keeping with other large studies that have investigated this hypothesis. However, other modifiable prognostic factors such as metformin and its effect on ovarian cancer tumor biology and survival are currently being researched.[27,28] Future studies include investigating a subset of obese patients who are taking metformin to evaluate their survival outcomes. Also, performing a metaanalysis of the existing data on obesity as a prognostic factor in ovarian cancer, because of the conflicting outcomes and relatively small sample sizes of the studies, should be done.

Clinical Practice Points

- Ovarian cancer is fifth leading cause of cancer deaths in women in the United States.
- Despite many advances in treatment over the past decade and the incorporation of new targeted therapies, the mortality remains essentially unchanged. Therefore, more studies have investigated modifiable prognostic factors that might improve treatment response, overall and progression-free survival.
- The role of obesity as a prognostic factor in ovarian cancer remains largely controversial.

- To our knowledge, this is one of the largest studies to date to investigate how obesity affects time to disease recurrence and progression-free survival in ovarian cancer.
- We concluded that despite the laboratory evidence supporting more aggressive tumor biology related to hormonal changes of obesity, there was no difference in the time to disease recurrence or progression-free survival between obese and nonobese patients.
- This would suggest that although obesity is related to many chronic illnesses, ovarian cancer recurrence is not negatively affected by this condition.

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Disclosure

The authors have stated that they have no conflicts of interest.

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